Leiden University
Medical Center

The Dutch guidelines for Marfan syndrome: 'between evidence and common sense'

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Outline

1. Introduction on Marfan clinics in the Netherlands
2. Quiz to test your knowledge about Marfan syndrome
3. Some Marfan facts and figures
4. Development of the Dutch Marfan guidelines
5. Marfan guidelines: evidence, expert opinion or common sense …
6. Conclusions and questions

The Marfan Quiz

Marfan clinics and DNA-diagnostics in the Netherlands

clinic

DNA

Groningen

Amsterdam (AMC)

Amsterdam (VUMC)

Leiden

Rotterdam

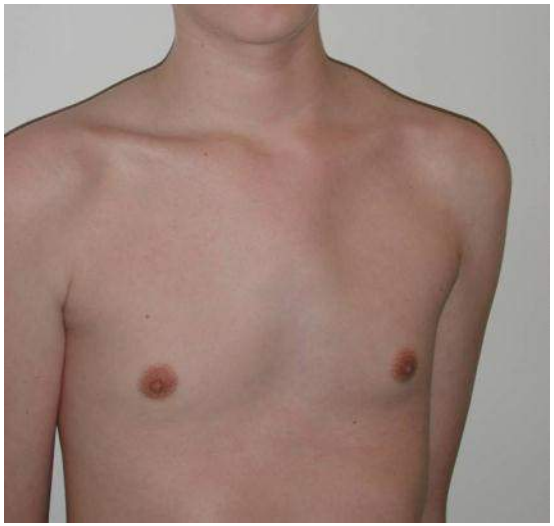
Nijmegen

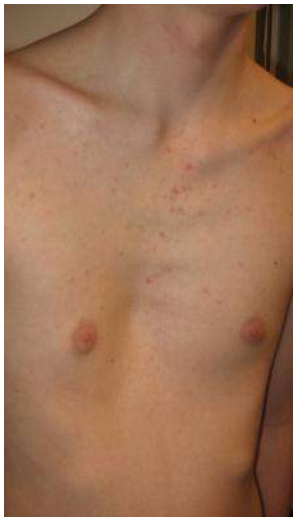
Maastricht

Marfan facts - Skeletal features

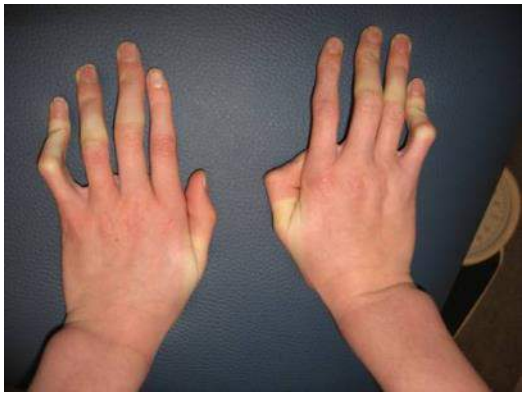
Pictures from National Marfan Foundation

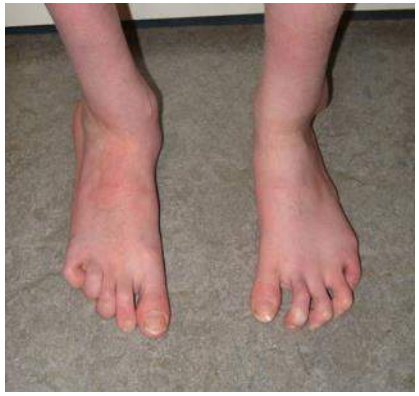
Tall stature with long limbs





Pectus deformities

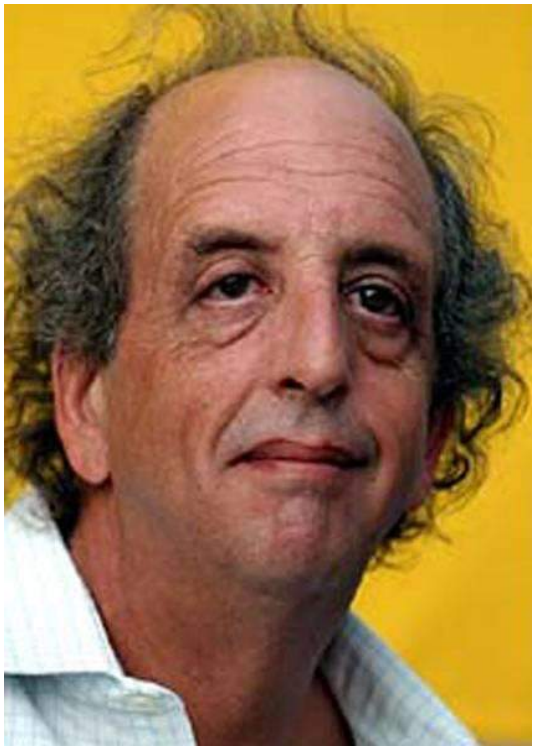




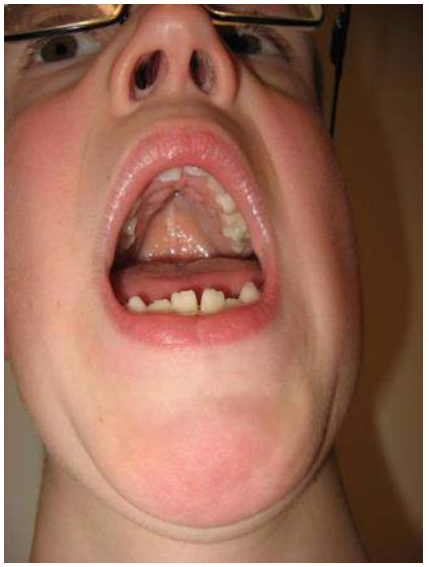
Arachnodactyly (spider fingers)

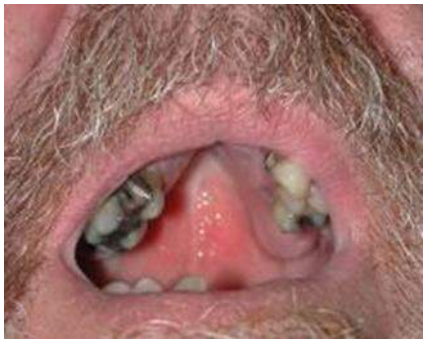
Flat feet with hindfoot deformity

Marfan facts - Facial characteristics



Vincent Schiavelli in "One flew over the cuckoo's nest"

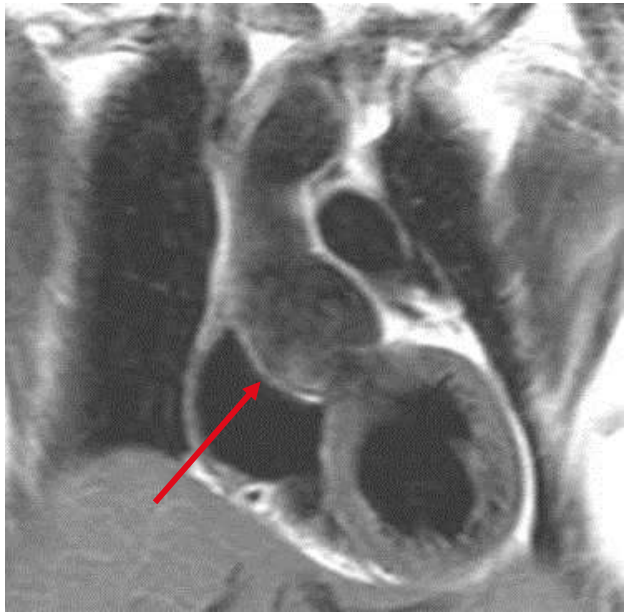


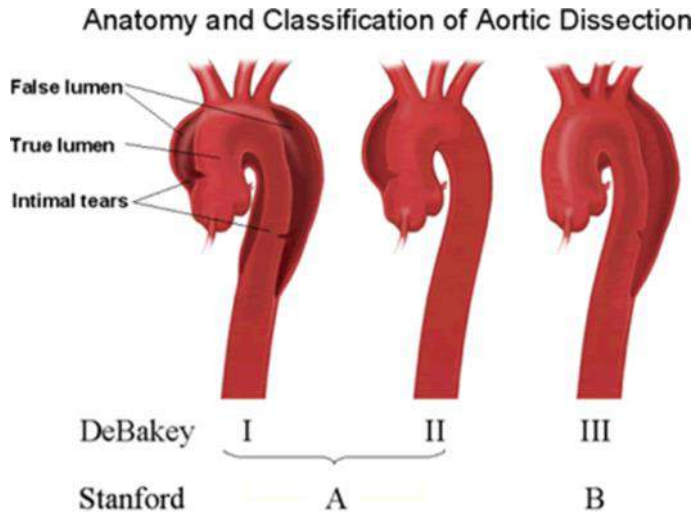


high palate and crowding of teeth

- downslant of palpebral fissures
- long face

Marfan facts - Cardiovascular features





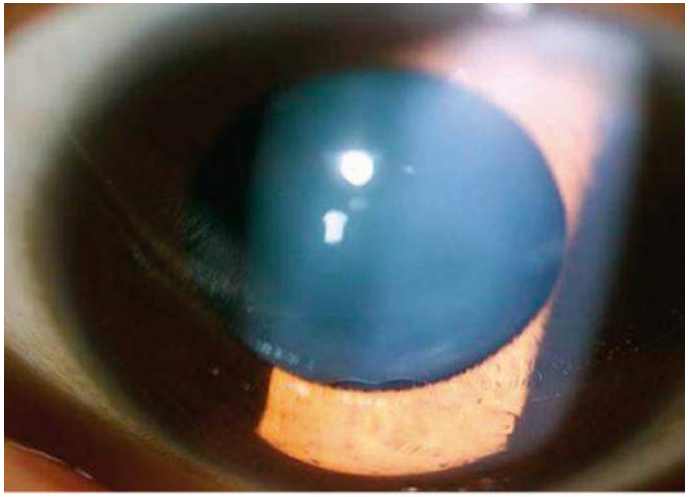
- 83 % aortic root dilatation and 88% MVP before age 25
- 20% cardiac surgery for aortic regurgitation or severe aortic root dilatation before age 25

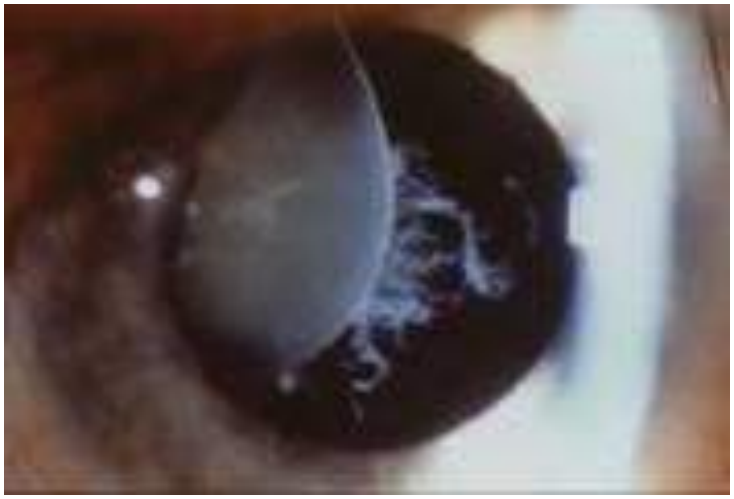
Survival from 40 to approximately 70 years

Marfan facts - Ophthalmologic features

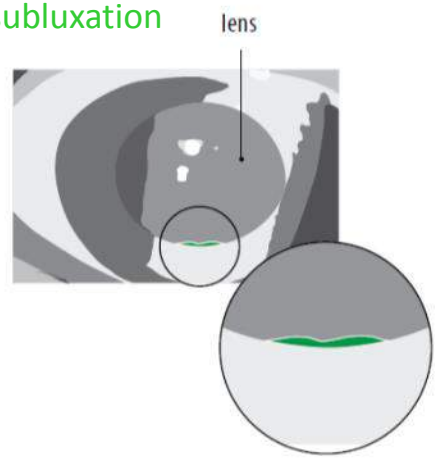
Ectopia lentis: 40-87%

Myopia> 3D bij 50%





subluxation



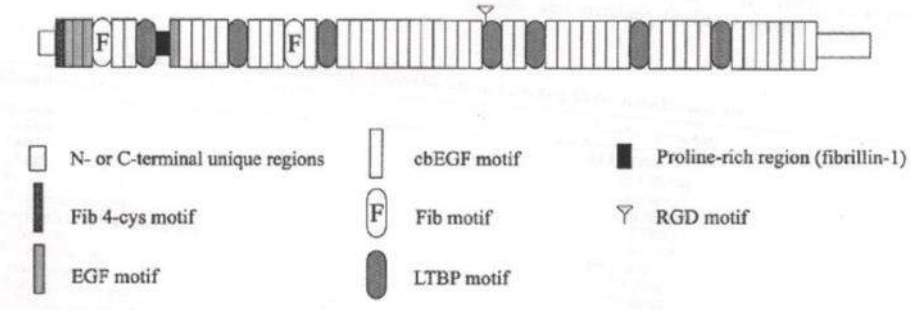
Marfan facts - Molecular aspects and pathogenesis

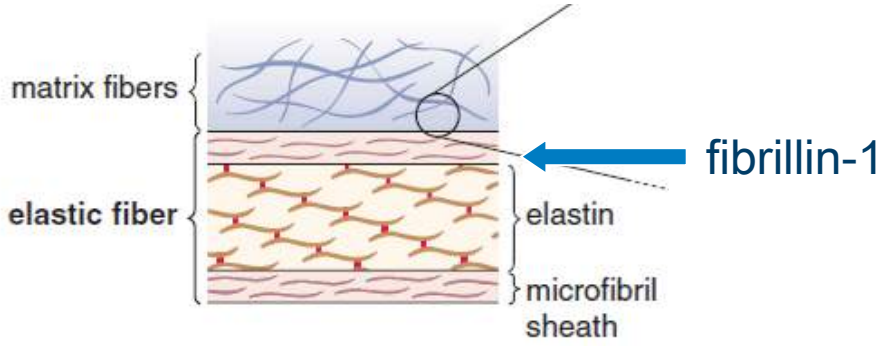
The gene: *FBN1*

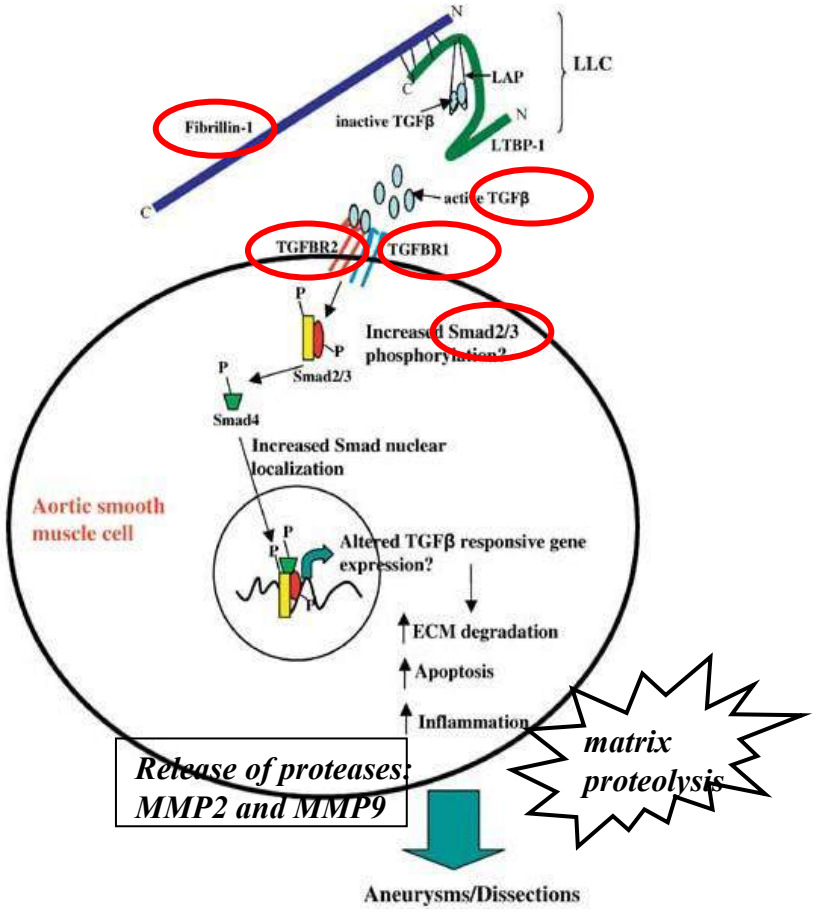
> 95% of Marfan

Autosomal dominant

25% de novo

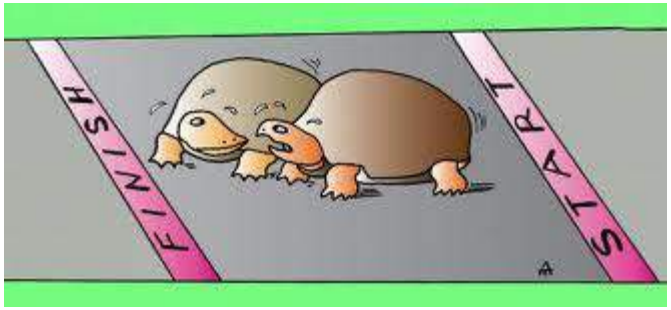






Development of the Dutch guidelines

Start in June 2010



Finish in December 2012

Why guidelines?

To create a tool for the provision of uniform care in Marfan syndrome

Referral

Diagnosis

Family studies

Treatment

Prenatal diagnosis

Surveillance

Pregnancy and delivery

Organization Marfan clinic

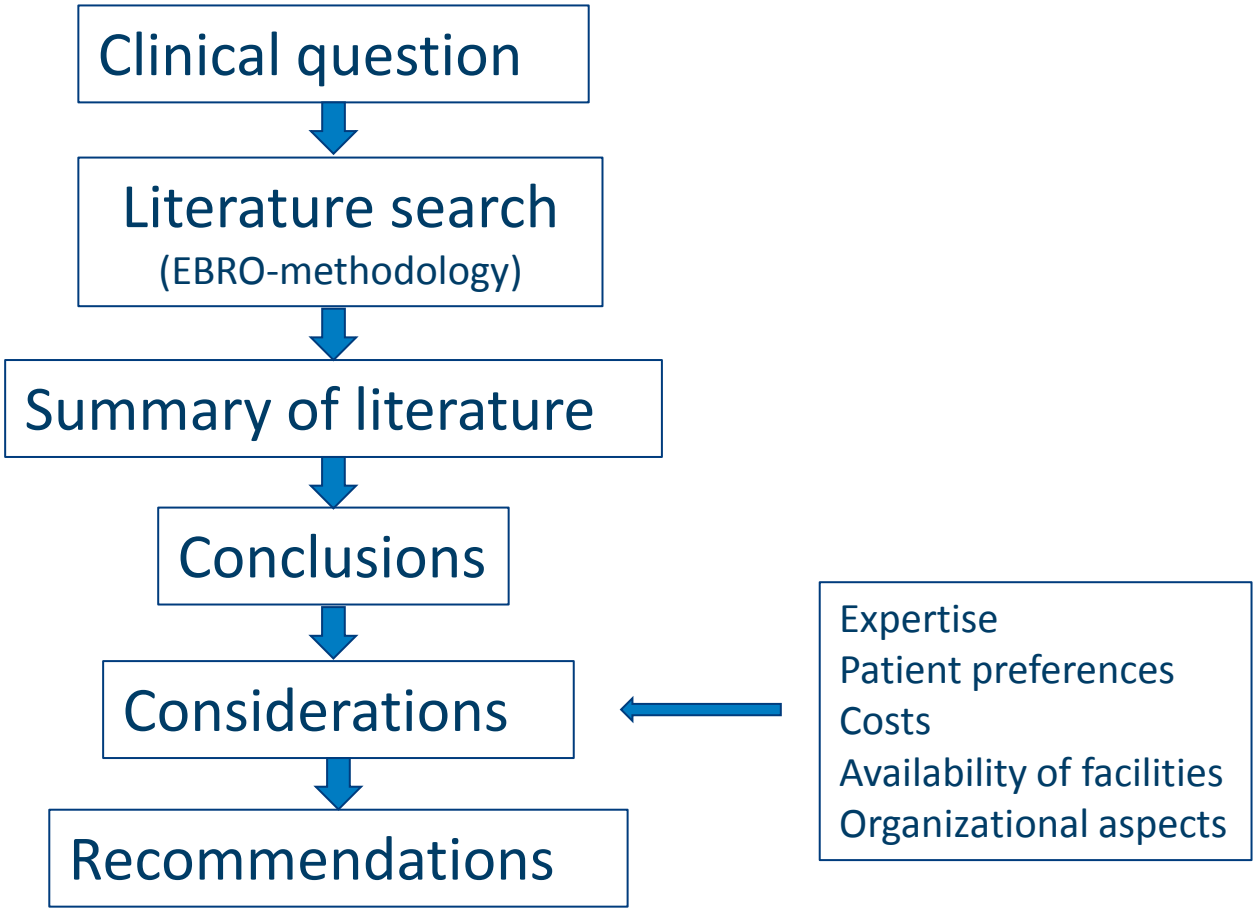
Working group

1. Cardiothoracic surgeon
2. Clinical geneticist
3. Gynaecologist
4. Cardiologist
5. Molecular geneticist
6. Pediatric cardiologist
7. Ophthalmologist
8. Orthopedic surgeon
9. Dutch patients association for Marfan syndrome

Methodologic support of a senior advisor of Dept of Professional Quality Support of the Dutch Federation of Medical Specialists (FMS)

Development of the guidelines

Appraisal of Guidelines for Research & Evaluation II" (AGREE II) instrument (www.agreecollaboration.org)



Evidence, expert opinion or common sense

Evidence according to the EBRO classification

Evidence level	Diagnostic accuracy of research
A1	Meta-analysis of two A2 studies
A2	Gold standard research: prospective, sufficient size, control group
B	Prospective but not with all features of A2, retrospective study or case-control study
C	Non comparative study

Conclusion based on	
1	One study A1 or two A2
2	One study A2 or two B
3	One study B or C
4	Expert opinion

Example: drug treatment (Ch7)

Clinical question

What's the effect of certain drugs on aortic growth?

Literature search and summary of literature

- ✓ *β-blokkers: positive effect but not conclusively proven*
- ✓ *Losartan: showed an positive effect in severe pediatric marfan patients*

Conclusions

- ✓ *β-blokkers:there are indications for an inhib. effect on the growth of the aorta*
- ✓ *Losartan: research just started, indication that it might work*

Considerations

- ✓ *Adverse effects*
- ✓ *No undisputable proof*

Recommendations

- ✓ *β -blockers: prescribe till more evidence*
- ✓ *Losartan: not proven yet, be conservative in prescribing*

The Dutch guidelines

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Who should be referred?

The basketball team

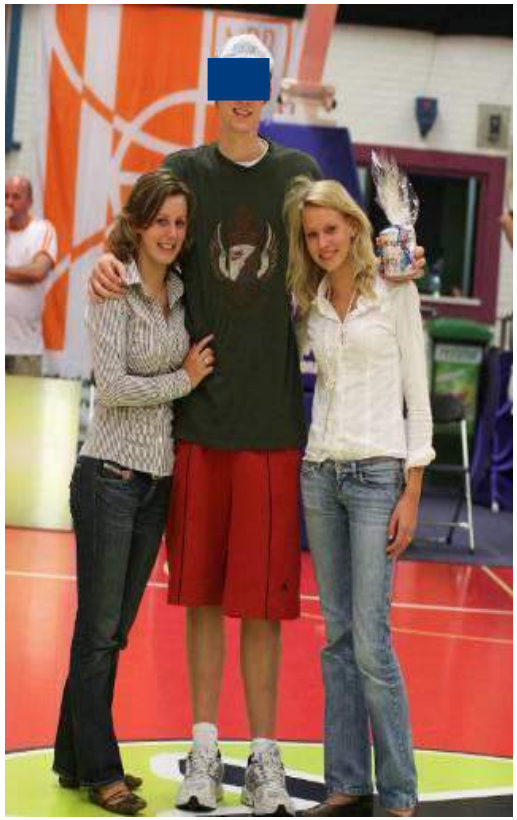
One of the mates of this basketball team died suddenly of an acute aortic dissection. The coach is worried, he heard this boy might have been affected with Marfan. He wants all players to be screened at a marfan clinic.

Question:

What is your advice?

A. You advice to screen all men just to be sure

B. You tell the coach not to worry. Marfan is a rare disorder, the chance that one of the team mates is affected is low



One of the men is still worried. Hij is tall and skinny but has no other marfanoid features. His family history is negative for aortic disease. He visits his GP.

Question:

What would be wise for the GP to advice?

A. Reassure

B. Only refer to a marfan clinic if there are more features

C. Always refer to a marfan clinic or expert

What's in the Dutch guidelines?

Recommendations *(Ch 3 Diagnostics)*

I. Refer all patients with the following features for assesment by a specialist in Marfan syndrome, preferably in association with a Marfan clinic:

- Aortic root dilatation or dissection of the thoracic aorta without obvious cause, or
- (Sub)luxation of the lens, or
- First-degree relative with Marfan syndrome.

II. Refer patients with **less specific features** of Marfan syndrome to an experienced specialist in Marfan syndrome, assessing the appropriate diagnostic route based on the features.

The Dutch guidelines

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Criteria for diagnosis and Z-scores

Diagnosis of Marfan syndrome

Original article

The revised Ghent nosology for the Marfan syndrome

Bart L Loeys,[1] Harry C Dietz,[2] Alan C Braverman,[3] Bert L Callewaert,[1]
Julie De Backer,[1] Richard B Devereux,[4] Yvonne Hilhorst-Hofstee,[5]
Guillaume Jondeau,[6] Laurence Faivre,[7] Dianna M Milewicz,[8] Reed E Pyeritz,[9]
Paul D Sponseller,[10] Paul Wordsworth,[11] Anne M De Paepe[1]

J Med Genet juni 2010

Diagnosis of Marfan syndrome

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:
(1) Ao ($Z \geq 2$) AND EL=MFS*
(2) Ao ($Z \geq 2$) AND *FBN1*=MFS
(3) Ao ($Z \geq 2$) AND Syst ($\geq$7pts)=MFS*
(4) EL AND *FBN1* with known Ao=MFS

Z-score of aortic root diameter

Mailonline Sept 2nd 2015

Sarah 40 yr was admitted to a marfanclinic because she is very tall, she has long fingers and a scoliosis. She has a disporportionate body habitus with long arms and legs.

Height 192 cm and weight **100 kg**

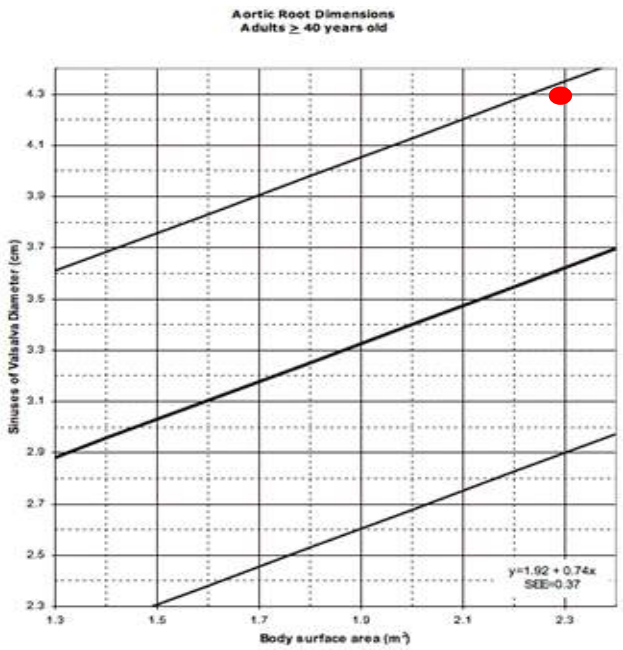
BSA: 2.3

Aortic root 43 mm

Systemic score 7

Eye examination normal

Your opinion



Z=+ 2

Z=0

Z=-2

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:
(1) Ao (Z ≥2) AND EL=MFS*
(2) Ao (Z ≥2) AND *FBN1*=MFS
(3) Ao (Z ≥2) AND Syst (≥7pts)=MFS*
(4) EL AND *FBN1* with known Ao=MFS

If you were the coördinating doctor of the marfanclinic, would you tell her:

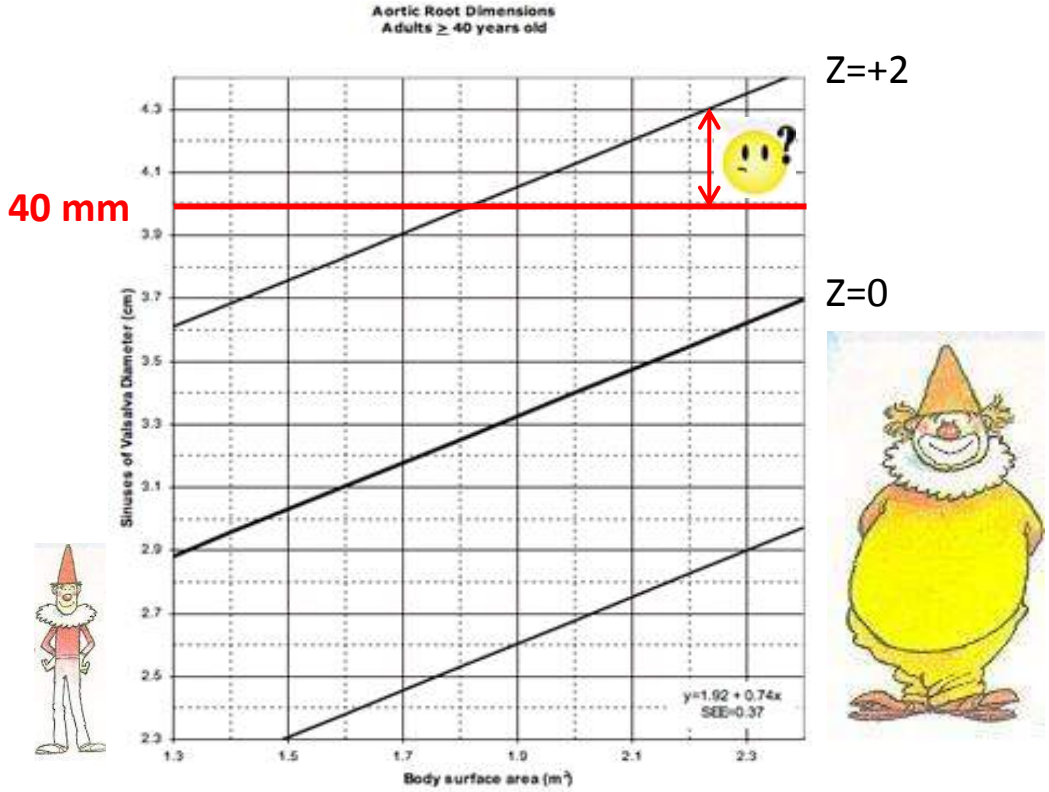
A. Not to worry, she does not fullfill the criteria for Marfan

B. She might have Marfan syndrome and you want to do further examinations

Z-score or absolute diameter?

Assumption of a linear relationship BSA – aortic root.

adult > 40 years old



Roman et al 1989

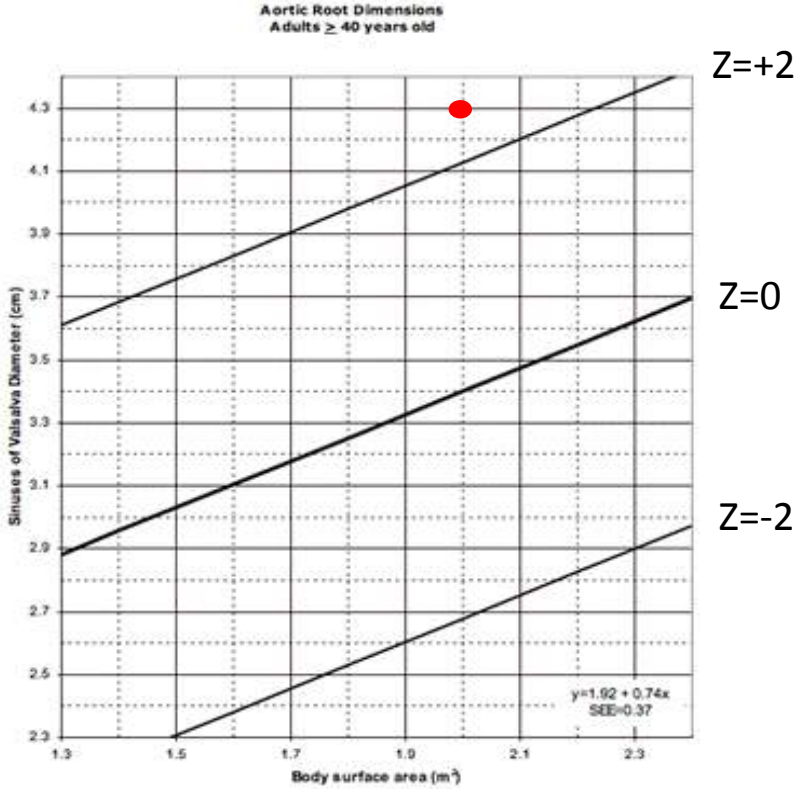
Z-score or absolute diameter?

Mailonline Sept 2nd 2015

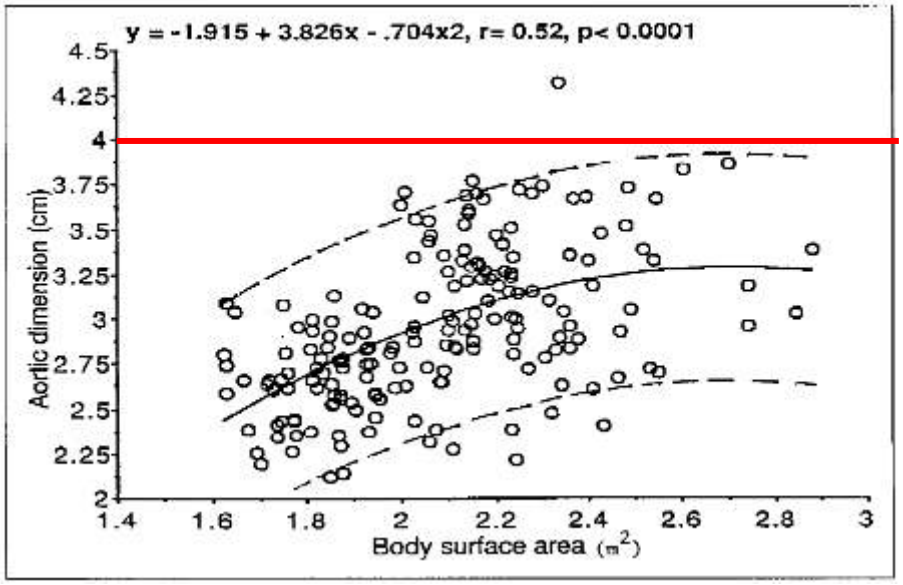
Sara lost a lot of weight, now she is 192 cm tall and **75 kg**

BSA: 2.0

Aortic root 43 mm **dilated**



Z-score or absolute diameter?



40 mm

Non-linear relation between aortic root and BSA in 1922 athletes.

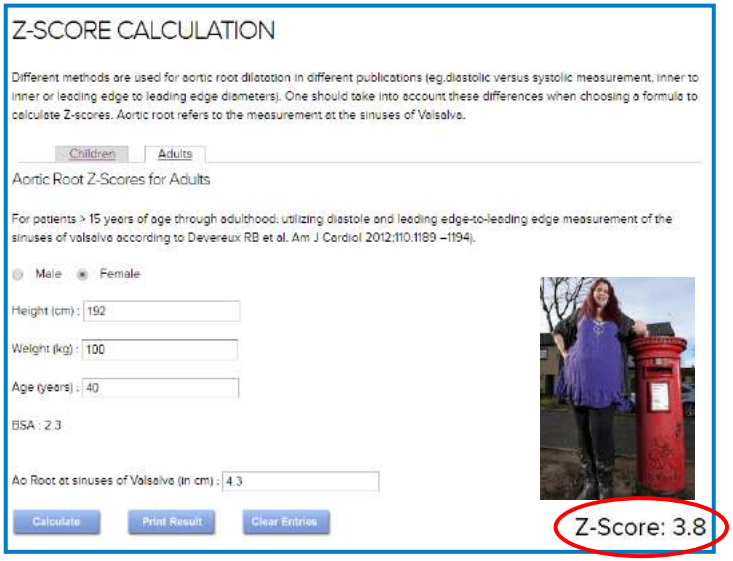
(Kinoshita et al. Am Heart J 2000)

New Z-scores

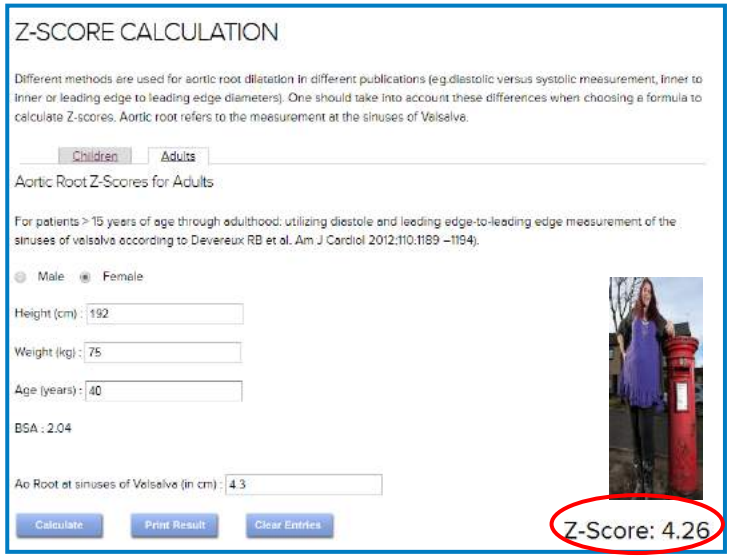
- Height seems to correlate more with aortic root diameter than weight
- In new Z-score calculators the Z-score is less influenced by body weight or BMI

Devereux, 2012; Van Kimmenade 2013

Big Sarah



Thin Sarah



Devereux, 2012, calculator on www.marfan.org

What's in the Dutch guidelines?

Recommendations (Ch 4 Diagnostic imaging aorta)

In an adult, an aortic root >40 mm should generally be regarded as dilated

- Smaller diameters may be considered abnormal depending on age, BSA and sex:
  - ✓ Shape of aortic root: pear
  - ✓ Ratio aortic root/ascending aorta
  - ✓ Z-scores may be helpful
- In children: use Z-scores

The Dutch guidelines

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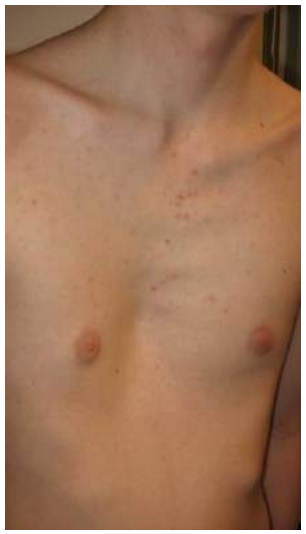
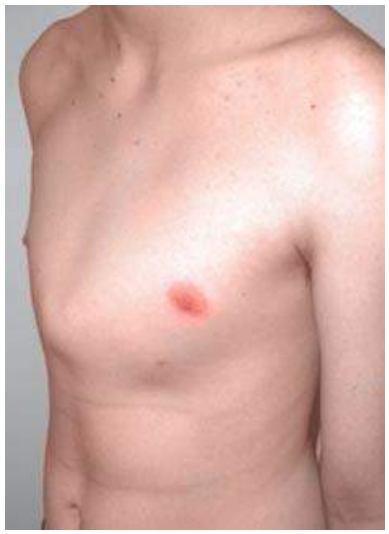
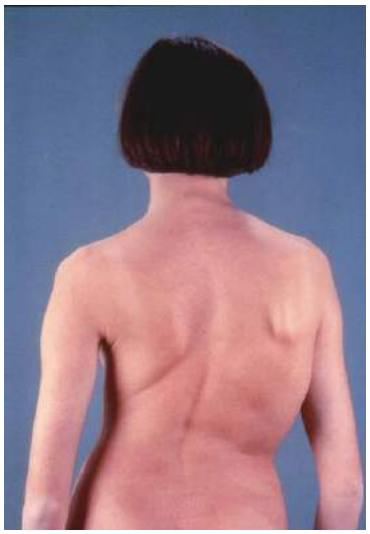
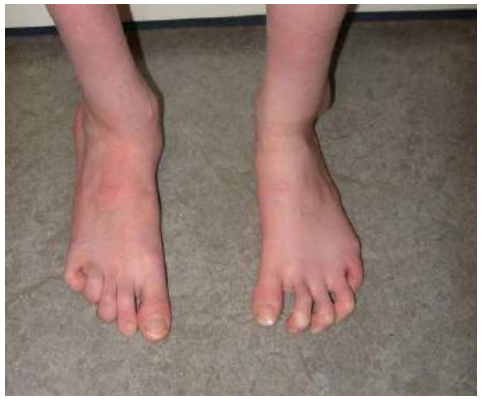
Is treatment different?

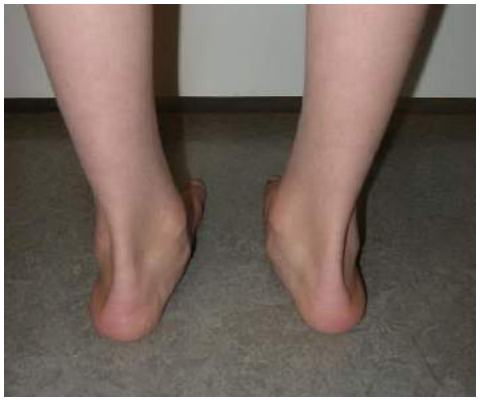
Treatment of skeletal abnormalities





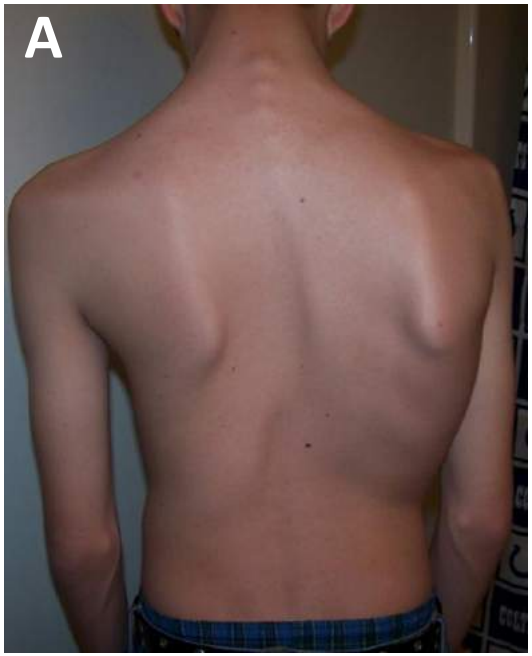






Should we treat musculoskeletal problems in Marfan patients different from non-Marfan patients?

Scoliosis



Boy 13 years old
Marfan syndrome
Spinal curve 30 degrees

Girl 13 years old
No Marfan syndrome
Spinal curve 30 degrees

Your opinion

Would you think that the scoliosis treatment for patient A with Marfan syndrome is different from patient B without Marfan syndrome?

A. YES

B. NO

What's in the Dutch guidelines?

Conclusions

Level 3	There are indications that, in Marfan patients with a still immature skeleton (Risser 2 or less) and scoliosis curves of between 20 and 45 degrees, wearing a brace can avoid the need for surgery in a small proportion of patients. *C* Sponseller et al., 2000; Birch & Herring, 1987
Level 3	There are indications that the percentage of patients in whom a brace can prevent surgery is lower in Marfan than in non-Marfan patients. *C* Sponseller et al. 2000; Birch & Herring, 1987
Level 4	There is insufficient available literature to justify treating other skeletal abnormalities in Marfan syndrome differently to those in patients without Marfan syndrome. *D* Opinion of the working group

What's in the Dutch guidelines?

Recommendations

In general, treat abnormalities of the musculoskeletal system in patients with Marfan syndrome in the same manner as for patients without Marfan syndrome.

In Marfan patients with scoliosis of between 20 and 45 degrees and a still immature skeleton, the (low) expected success rate of a brace should be weighed against the discomfort and the advantages and disadvantages of an operation.

Ch 6 Treatment skeletal abnormalities

The Dutch guidelines

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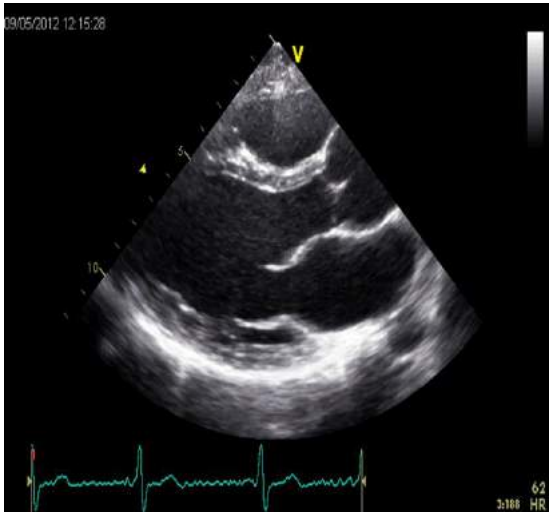
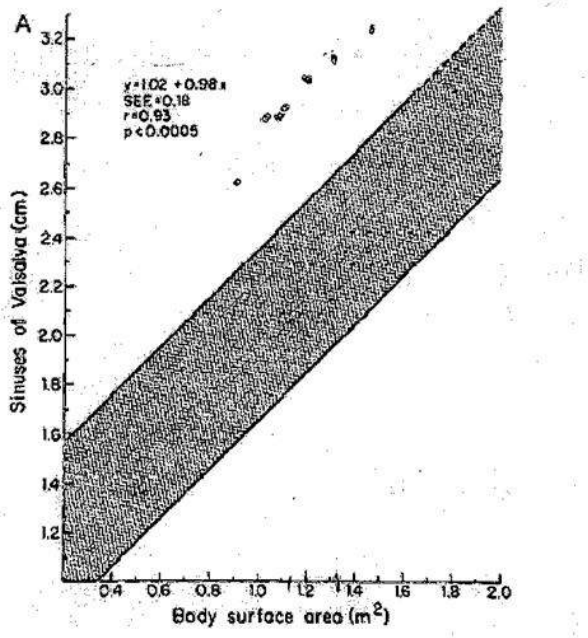
What are the restrictions?

Lifestyle recommendations



Emma 13 years old was diagnosed with Marfan syndrome after her father suffered from an acute aortic dissection at age 40 years.

She is a quite fanatic competition swimmer.



Your opinion

Emma was bullied at the elementary school because of her glasses and her body habitus. She was very tall and skinny. After she started swimming she got stronger and more confident.

Do you advice Emma to quit her sport?

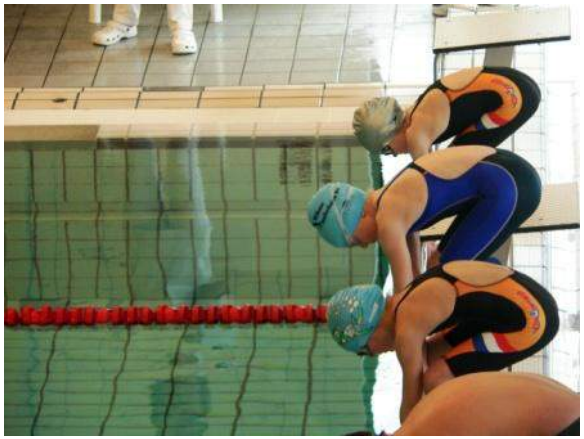
A. Yes
B. No

What's in the Dutch guidelines?

Recommendations Ch 14 Life style recommendations:

Caution should be exercised with regard to **competitive sports**, **major peaks of exertion** and intensive static exertion.

Participation in recreational low-to-moderate intensity exercise can usually be allowed.



advice against competitive swimming!

Did the doctor allow Emma to do competitive swimming?

International guidelines based on:

- Expert opinion
- Theoretical considerations
- Retrospective observations

Emma and her parents were informed about the guidelines and together they decided that she was allowed **to keep on swimming with stringent follow up at de child cardiologist.**

Inform patient and individalize advice

Conclusions

- The Dutch guidelines provide a tool to provide uniform care for Marfan patients
- The care for Marfan patients is largely based on expert opinion and common sense
- Guidelines are a guide, the care should be tailored for every patient
- Future research will hopefully provide evidence for several aspects in diagnosis, therapy and surveillance

Acknowledgements

Working group

J.M. Cobben, clinical geneticist

M. Kempers, clinical geneticist

J. Lind, gynaecologist

B.J. Mulder, cardiologist

G. Pals, molecular geneticist

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M.A. Pols, senior advisor

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B.J. van Royen, orthopedic surgeon

J. Timmermans, cardiologist

J.P. van Tintelen, cinical geneticist

Patient support group

F.M.L.J. Oorthuys, former chair patient support group

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